A 3D Generative Model for Structure-Based Drug Design

Year: 2022 | Citations: 235 | Authors: Shitong Luo

Abstract

We study a fundamental problem in structure-based drug design -- generating molecules that bind to specific protein binding sites. While we have witnessed the great success of deep generative models in drug design, the existing methods are mostly string-based or graph-based. They are limited by the lack of spatial information and thus unable to be applied to structure-based design tasks. Particularly, such models have no or little knowledge of how molecules interact with their target proteins exactly in 3D space. In this paper, we propose a 3D generative model that generates molecules given a designated 3D protein binding site. Specifically, given a binding site as the 3D context, our model estimates the probability density of atom's occurrences in 3D space -- positions that are more likely to have atoms will be assigned higher probability. To generate 3D molecules, we propose an auto-regressive sampling scheme -- atoms are sampled sequentially from the learned distribution until there is no room for new atoms. Combined with this sampling scheme, our model can generate valid and diverse molecules, which could be applicable to various structure-based molecular design tasks such as molecule sampling and linker design. Experimental results demonstrate that molecules sampled from our model exhibit high binding affinity to specific targets and good drug properties such as drug-likeness even if the model is not explicitly optimized for them.